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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/810,883	THOMAS ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *10-13,15-17 and 20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,14,18,19 and 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the restriction requirement received on 4/30/03 has been entered. Claims 1-28 are pending in the instant application. Of these, claims 10-13, 15-17, and 20-23 are withdrawn from prosecution as being drawn to subject matter non-elected without traverse in paper no. 7., see below. Claims 1-9, 14, 18-19, and 24-28 are currently under examination. An action on the merits follows.

Election/Restriction

Applicant's election of Group I, claims 1-9, 14, 18-19, and 24-28, in Paper No. 7, is acknowledged. In regards to claims 18-19, these claims are multiply dependant claims which depend on two separate inventions. These claims have only been examined insofar as they depend on elected claim 14. The alternative embodiments of claims 18-19, insofar as they depend on non-elected claims 15 and 16, have not been examined. As the applicant has not presented arguments traversing the grounds of restriction, the restriction requirement is deemed proper and made FINAL.

35 U.S.C. 132

The amendment filed on 6/15/01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new

matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment added new claims 25 and 28 which recite wherein the bispecific antibody binds to FcεRII. The original disclosure filed on 3/16/01 does not disclose FcεRII or antibody against FcεRII.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 14, 18-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification discloses bispecific molecules comprising a first determinant that targets an ITAM and a second determinant that targets an ITIM. The specification does not disclose or provide any written description for "determinants" other than antibodies or antibody fragments which recognize an ITAM and an ITIM . The specification discloses several ITAM molecules and two ITIM molecules and indicates that antibodies to these

molecules can be used in the instant vectors and methods. The specification, however, fails to specifically identify or disclose any non-antibody "determinant" which is capable of binding to an ITAM or ITIM. Further, the specification fails to provide sufficient description of the physical or chemical properties of any non-antibody determinant which binds to an ITAM or ITIM such that molecules which meet these requirements could be identified. Based on the breadth of the claims as written, which encompass non-protein, protein-based and antibody "determinants" capable of binding to an ITAM and ITIM, the specification lacks written description for the identity of any determinant meeting these requirements other than an antibody or antibody fragment.

Vas-Cath Inc. V. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of 'written description' inquiry, whatever is claimed" (see page 1117). In addition, the Revised Interim Guidelines state " when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus .....In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). By failing to identify or describe any determinant other than an antibody, the specification does not "clearly allow persons or ordinary

skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that an element is part of the invention. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of molecules which comprise "determinants" of bispecific molecules capable of coligating an ITAM and an ITIM. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-9, 14, and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification discloses bispecific molecules comprising a first determinant that targets an ITAM and a second determinant that targets an ITIM. The specification further discloses methods of treating allergy by administering molecules *in vivo*.

The specification does not provide an enabling disclosure for making and using bispecific molecule which encompasses "determinants" which are not derived from antibodies. As discussed in detail in the above rejection of the claims for lack of written description, the specification

discloses several target ITAM molecules and two ITIM molecules and indicates that antibodies to these molecules can be used in the instant vectors and methods. The specification, however, fails to specifically identify or disclose any non-antibody "determinant" which is capable of binding to an ITAM or ITIM. Further, the specification fails to provide sufficient description of the physical or chemical properties of any non-antibody determinant which binds to an ITAM or ITIM such that molecules which meet these requirements could be identified. Based on the breadth of the claims as written, which encompass non-protein, protein-based and antibody "determinants" capable of binding to an ITAM and ITIM, the specification lacks sufficient guidance for the identity of any determinant meeting these requirements other than an antibody or antibody fragment.

The specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). 35 U.S.C. § 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific** starting material **or of any of the conditions under which a process can be**

> **carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Therefore, based on the failure of the specification to identify or adequately describe any molecular "determinant" other than an antibody or antibody fragment capable of binding to an ITIM or ITAM, the failure of the specification to disclose methods of making bispecific molecules which are not bispecific antibodies, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 14, and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 5 and 19 depend on claims 1 or 14 respectively and further recite the limitation wherein the first determinant targets IgE or an allergen. Claims 1 and 14 recite that the first determinant targets an ITAM module. Neither the literature nor the specification teach that the IgE antibody or an allergen contain an ITAM module. Thus, it is confusing how IgE or an allergen which do not comprise an ITAM module can be the target of

the first determinant. Furthermore, it is unclear whether an "ITAM" or "ITIM" module refers to the actual ITAM or ITIM motif contained in an immunoreceptor or whether the applicant intends to encompass determinants that bind to the entire immunoreceptor molecule which comprises the ITAM or ITIM module. Therefore, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 7-9, 14, 24, and 26-27 are rejected under 35 U.S.C. 102(a) as being anticipated by EP 0 861 891 A1. (1998), hereafter referred to as Daeron et al. The applicant claims a bispecific molecule or antibody which targets an ITAM and an ITIM. The applicant further claims said bispecific compositions wherein the ITAM and ITIM are on mast cells or basophils, and wherein the bispecific molecule or antibody inhibits the release of TNF-α from the mast cells or basophils. In addition, the applicant claims pharmaceutical compositions of said

bispecific molecules, and methods of administering said molecules or antibodies to a patient to treat allergic disease or to inhibit TNF-α release by mast cells.

Daeron et al. teaches bispecific molecules which include bispecific antibodies that are capable of cross-linking a stimulatory ITAM receptor and a KIR or KIR homologue such as gp49B1 (Daeron et al., pages 14-15, claims 1-15). Daeron et al. further teaches that KIRs and gp49B1 contain ITIM domains and that cross-linking of the ITAM and ITIM on a mast cell results in the modulation of TNF-α release (Daeron et al., page 14-15, especially claim 15). Daeron et al. further teaches pharmaceutical compositions comprising said bispecific molecules and the use of the bispecific molecules to treat allergy and to modulate TNF-α release (Daeron et al., pages 3-4). Thus, by teaching all the limitations of the claims as written, Daeron et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 861 891 A1. (1998), hereafter referred to as Daeron et al., as applied to claims 1, 2, 7-9, 14, 24, and 26-27 under 35 U.S.C. 102(a) above, in view of Arm et al. (1997) J. Immunol., Vol. 159, 2342-2349. The applicant claims a bispecific molecule or antibody which targets an ITAM and an ITIM. The applicant further claims said bispecific compositions wherein the ITAM and ITIM are FceRI and HM18 respectively. In addition, the applicant claims methods of administering said bispecific molecules to a patient to treat allergic disease.

Daeron et al. teaches bispecific molecules which include bispecific antibodies that are capable of cross-linking a stimulatory ITAM receptor such as FcεRI and a KIR or KIR homologue such as gp49B1 (Daeron et al., pages 14-15, claims 1-15). Daeron et al. further teaches that KIRs and gp49B1 contain ITIM domains and that cross-linking of the ITAM and ITIM on a mast cell results in the modulation of TNF-α release (Daeron et al., page 14-15,

especially claim 15). Daeron et al. further teaches pharmaceutical compositions comprising said bispecific molecules and the use of the bispecific molecules to treat allergy and to modulate TNF-α release (Daeron et al., pages 3-4).

Daeron et al. differs from claims 4 and 18 in not specifically reciting that the ITIM is HM18. Arm et al. supplements Daeron et al. by teaching that HM18 is found on human mast cells and is the human homolog of gp49B1 (Arm et al., 2343-2345). Arm et al. further teaches that HM18 contains an ITIM domain and transduces signals in a manner analogous to gp49B1 (Arm et al., page 2349). In addition, Arm et al. teaches antibodies specific for HM18 (Arm et al., page 2344-2345). Therefore, based on the motivation to use a bispecific antibody to cross-link an ITAM receptor such as FcεRI with an ITIM receptor such as KIR homolog, and most specifically gp49B1, in order to modulate mast cell cytokine release and treat allergic conditions provided by Daeron et al., and the teachings of Arm et al. that HM18 is the human homolog of gp49B1 on human mast cells, it would have been *prima facie* obvious to the skilled artisan at the time of filing to cross-link an ITAM and HM18 on human mast cells using a bispecific antibody that recognizes FcεRI and HM18. Further, based on the teachings of Arm et al. of antibodies specific for HM18, and the teaching of Daeron et al. for making bispecific antibodies, the skilled artisan would have had a reasonable expectation of success in making a bispecific antibody capable of cross-linking an ITAM such as FcεRI and ITAM such as HM18.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 861 891 A1. (1998), hereafter referred to as Daeron et al., as applied to claims 1, 2, 7-9, 14, 24, and 26-27 under 35 U.S.C. 102(a) above, in view of U.S. Patent No. 5,530,101 (1996), hereafter referred to as Queen et al. The applicant claims a bispecific molecule or antibody which targets an ITAM and an ITIM, wherein at least one determinant is a humanized antibody or fragment thereof.

Daeron et al. teaches bispecific antibodies that are capable of cross-linking a stimulatory ITAM receptor such as FcεRI and a KIR or KIR homologue such as gp49B1 (Daeron et al., pages 14-15, claims 1-15, especially claim 11). Daeron et al. further teaches that KIRs and gp49B1 contain ITIM domains and that cross-linking of the ITAM and ITIM on a mast cell results in the modulation of TNF-α release (Daeron et al., page 14-15, especially claim 15). Daeron et al. further teaches pharmaceutical compositions comprising said bispecific molecules and the use of the bispecific molecules to treat allergy and to modulate TNF-α release (Daeron et al., pages 3-4).

Daeron et al. differs from claim 3 in not specifically teaching the use of a humanized antibody or bispecific antibody. Queen et al. supplements Daeron et al. by teaching the use of non-human antibodies in human patients is adversely affected by immune responses against the foreign antibodies. Queen et al. teaches that such deleterious immune responses can be avoided by making "humanized" antibodies (Queen et al., columns 1-2). Queen et al. further provides substantial guidance as to methods of making humanized antibodies (Queen et al., columns 10-68). Therefore, based on the motivation to use "humanized" antibodies in patients as taught by

Queen et al., it would have been *prima facie* obvious to the skilled artisan to use at least one humanized antibody as part of the bispecific antibody taught by Daeron et al. in order to avoid deleterious immune responses in the patient. Further, in view of the substantial guidance provided by Queen et al., the skilled artisan would have had a reasonable expectation to success in making a "humanized" bispecific antibody which recognizes and ITAM and an ITIM.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

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